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*BY HAND DELIVERY*

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Docket No. 04P-0157**
**Comments to Suitability Petition**

Dear Sir or Madam:

We are writing on behalf of GlaxoSmithKline (GSK) regarding the above-referenced suitability petition, submitted by The Weinberg Group on April 1, 2004. This petition seeks a determination that amoxicillin/clavulanate potassium 200 mg/28.5 mg and 400 mg/57 mg tablets for oral suspension are suitable for submission in an abbreviated new drug application (ANDA). The reference product cited in the petition is GSK's Augmentin® chewable tablets.

According to the Food and Drug Administration (FDA), if the change proposed in a suitability petition does not qualify for a full waiver of pediatric studies under the Pediatric Research Equity Act (PREA), that petition will be denied, because clinical studies will be required to demonstrate the safety and/or effectiveness of the change. The Weinberg Group's suitability petition fails to qualify for such a waiver. For this reason, and for the other reasons discussed below, the petition must be denied.

## I. Background

On September 10, 2002, The Weinberg Group submitted to FDA a suitability petition, seeking a determination that amoxicillin/clavulanate potassium 200 mg/28.5 mg, 400 mg/57 mg, and 600 mg/42.9 mg tablets for oral suspension are suitable for submission in ANDAs. *See* Docket No. 02P-0406 (the 2002 Petition); *see*

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*also* 21 USC 355(j)(2)(C); 21 CFR 314.93. The reference listed drugs (RLDs) cited in the petition were Augmentin® and Augmentin ES-600® powder for oral suspension.

On December 19, 2002, GSK submitted comments in opposition to this petition. GSK noted that in addition to a change in dosage form, The Weinberg Group also sought a change in the approved dosing regimen, because tablets for oral suspension cannot be dosed in the precise, mg/kg increments offered by GSK's powder for oral suspension. As explained in GSK's comments, besides being impermissible under a suitability petition, The Weinberg Group's proposed change would require clinical study and substantial re-labeling of the reference products.

The Weinberg Group replied to GSK's comments on May 16, 2003, and submitted additional comments on November 19, 2003. In the latter comments, The Weinberg Group reported that FDA had indicated the proposed 200 mg/28.5 mg and 400 mg/57 mg tablets for oral suspension may be suitable for submission in an ANDA, if the RLD were changed to Augmentin® chewable tablets. On January 30, 2004, GSK replied to this submission, supporting FDA's apparent decision to deny The Weinberg Group's petition, insofar as it sought permission to submit ANDAs referencing GSK's powder for oral suspension products.

Shortly thereafter, FDA issued a letter to The Weinberg Group, stating that review of its petition could not continue, unless required pediatric studies were waived. According to FDA, the recently-enacted PREA requires that all applications for new active ingredients, indications, dosage forms, or routes of administration include assessments of the safety and effectiveness of the products in all relevant pediatric populations. *See* Letter from G. Buehler to N. Fleischer, Ph.D., Docket No. 02P-0406 (Feb. 3, 2004) (PREA Letter); *see also* Pub. L. No. 108-155, 117 Stat. 1936 (2003) (codified at 21 USC 355c).

FDA informed The Weinberg Group that its suitability petition is subject to this requirement. "If the changed proposed in an ANDA suitability petition does not qualify for a full waiver of the pediatric studies," the agency wrote, "that petition will be denied because, under PREA, clinical studies are required to demonstrate the safety and or effectiveness of the change . . . ." PREA Letter.[1]

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1 FDA's application of the PREA to suitability petitions is consistent with its practice under its invalidated "Pediatric Rule." *See* 63 FR 66632, 66641 (Dec. 2, 1998) ("FDA notes that petitions submitted under section 505(j)(2)(C) . . . may be denied if 'investigations must be conducted to show the safety and effectiveness of the change."); Draft Guidance for Industry: *Recommendations for Complying with the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))* 3 (Nov. 2000) ("Applications for

In response, The Weinberg Group submitted to FDA a request for a full waiver of pediatric studies. *See* Amendment to Petition, Docket No. 02P-0406 (Mar. 10, 2004) (Pediatric Waiver Request). The Weinberg Group argued that its proposed products do not represent a meaningful therapeutic benefit for, and would not likely be used in a substantial number of, pediatric patients. *See id.; see also* 21 USC 355c(a)(4)(A)(iii).

Finally, on April 1, 2004, The Weinberg Group withdrew from the 2002 Petition its request for a determination that amoxicillin/clavulanate potassium 200 mg/28.5 mg and 400 mg/57 mg tablets for oral suspension are suitable for submission in an ANDA. Rather, The Weinberg Group submitted a new suitability petition for this product, citing Augmentin® chewable tablets as the RLD. *See* Docket No. 04P-0157 (Apr. 1, 2004) (the 2004 Petition). Included in this new petition is a second request for a full waiver of required pediatric studies. The Weinberg Group's earlier petition, concerning 600 mg/42.9 mg tablets for oral suspension, remains pending.

## II. The Weinberg Group's Suitability Petition Does Not Qualify for a Full Waiver Under the Pediatric Research Equity Act

Under the Pediatric Research Equity Act, FDA may grant a full waiver of pediatric studies if a drug: "(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; *and* (II) is not likely to be used in a substantial number of pediatric patients." 21 USC 355c(a)(4)(A)(iii) (emphasis added). Because The Weinberg Group's suitability petition does not qualify for a waiver under this standard, it must be denied; clearly, clinical studies will be required to demonstrate the safety and/or effectiveness of the proposed change. *See* PREA Letter.[2]

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drugs that are not duplicates of already approved products are required to comply with the rule. This includes applications submitted under 505(j)(2)(C) suitability petitions . . . .").

2 The PREA also provides for a full waiver of pediatric studies if such studies are impossible or highly impracticable, or if there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric populations. *See* 21 USC 355c(a)(4)(A). The Weinberg Group does not argue that its suitability petition qualifies for a waiver under either of these standards.

*A. The Benefit from The Weinberg Group's Proposed Product Is Directed to the Pediatric Population*

In its first waiver request, The Weinberg Group claimed that its products provide "a more convenient dosage form" with respect to unit-dose dispensing, ease of administration to patients who have difficulty swallowing, and storage. Pediatric Waiver Request at 2. The Weinberg Group made a similar argument in its new petition, stating that its product is more convenient for patients who have difficulty with chewable tablets, or who prefer a liquid dosage form. *See* 2004 Petition at 3. Nevertheless, The Weinberg Group stated that these products do not represent a meaningful therapeutic benefit for pediatric patients, because these benefits, "while not excluding pediatrics, are directed to the adult population." Pediatric Waiver Request at 2; *accord* 2004 Petition at 3.

GSK disagrees with the assertion that the potential benefits of the tablet for oral suspension dosage form "are directed to the adult population." Augmentin® is used widely in the pediatric population, for acute otitis media (AOM), sinusitis, and other common pediatric infections. Also, children often are unable or unwilling to chew and/or swallow tablets, which can lead to compliance concerns and sub-therapeutic dosing. Ranbaxy Pharmaceuticals cited increasing compliance in such children as a primary reason for its development of DisperMox™ (amoxicillin) 200 and 400 mg tablets for oral suspension. *See* Press Release (Nov. 3, 2003) (attached at Tab 1). Clearly, The Weinberg Group's proposed product is primarily directed to pediatric patients.

*B. The Weinberg Group's Proposed Product is Likely to be Used in a Substantial Number of Pediatric Patients*

In its first waiver request, The Weinberg Group acknowledged that its proposed products would be approved for use in pediatric patients, 3 months of age and older, within the correct weight range for dosing. "Based on the limited pediatric patient population," however, The Weinberg Group claimed that "there will not be substantial use of the product in pediatric patients, and therefore does not warrant a pediatric study." Pediatric Waiver Request at 5. The Weinberg Group did not address this requirement for a waiver in its more recent suitability petition. *See* 2004 Petition.

The assertion that The Weinberg Group's proposed product will not be used in a substantial number of pediatric patients is implausible. As noted above,

Augmentin® is used widely in pediatric populations, and its approved labeling contains specific instructions for dosing the product to children. *See* Augmentin® Labeling, *Dosage and Administration* (2004) (attached at Tab 2). Moreover, Ranbaxy's press release announcing the availability of amoxicillin 200 and 400 mg tablets for oral suspension states that AOM is the most common cause of pediatric office visits in the United States, exceeding 35 million in 2001. *See* Tab 1.

## III. The Weinberg Group's Suitability Petitions Continue to Raise Questions of Safety and Effectiveness

By changing the reference product for its 200 mg/28.5 mg and 400 mg/57 mg tablets for oral suspension to Augmentin® chewable tablets, The Weinberg Group has addressed several concerns regarding the inability of a tablet for oral suspension to replicate the precise, mg/kg increments offered by a powder for oral suspension. Nevertheless, questions regarding the use of this dosage form remain. GSK presented to FDA several of these concerns in its comments to The Weinberg Group's original suitability petition. *See* Comments to Petition, Docket No. 02P-0406 (Dec. 19, 2002) at 6-7.

There currently are no standards in place regarding the labeling or use of a tablet for oral suspension dosage form. The instructions proposed by The Weinberg Group – "[m]ix one tablet in a small amount of water" – likely have not been tested in usage studies. *See* 2004 Petition, Tab 2 at 11. Caregivers may not recognize whether they have properly reconstituted the product, and may require more guidance, including patient-specific labeling, to ensure proper usage. Actual usage or labeling comprehension studies may be needed before the safety and/or effectiveness of this dosage form can be assured. *See* Petition Response, Docket No. 01P-0302 (Apr. 12, 2002) (denying a suitability petition in part on the need for clinical studies in an actual use setting).

At minimum, FDA should develop guidance regarding the labeling and use of a tablet for oral suspension dosage form. Until such guidance is issued, the agency should not continue to approve suitability petitions and ANDAs for tablet for oral suspension products, which do not contain clinical data demonstrating the products' safe and effective use.

## IV. Conclusion

The Weinberg Group acknowledged in its requests for a full waiver of pediatric studies that, under the PREA, it must be shown that the drug does not represent a meaningful therapeutic benefit over existing therapies *and* is not likely to be used in a substantial number of pediatric patients. The Weinberg Group's requests, however, plainly fail to meet these requirements. As recognized by FDA, this mandates denial of the suitability petition itself, because clinical studies will be required to demonstrate the safety and/or effectiveness of the proposed change. Finally, FDA should not continue to approve petitions and ANDAs for tablet for oral suspension products, until issuing guidance regarding the labeling and use of this novel dosage form.

Sincerely,

David M. Fox
Hogan & Hartson L.L.P.

Attachments

cc: Gary Buehler, Director, Office of Generic Drugs, HFD-600
Martin Shimer, Senior Regulatory Manager, HFD-615
Emily Thakur, Project Manager, HFD-615